

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 5199-152PCT		Date of mailing (day/month/year) 26 JUN 2007
International application No. PCT/US05/05877		FOR FURTHER ACTION See paragraph 2 below
International filing date (day/month/year) 22 February 2005 (22.02.2005)	Priority date (day/month/year) 26 February 2004 (26.02.2004)	
International Patent Classification (IPC) or both national classification and IPC IPC: C12N 5/02(2006.01),5/06(2006.01),5/08(2006.01) USPC: 435/377,325,368,375		
Applicant THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF		

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the opinion |
| <input type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input checked="" type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

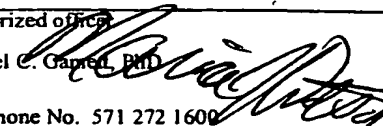
2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Date of completion of this opinion 11 June 2007 (11.06.2007)	Authorized officer  Daniel C. Garnett, PhD Telephone No. 571 272 1600
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Form PCT/ISA/237 (cover sheet) (April 2005)

Applicants: Thomas M. Jessell, et al.
Serial Number: 10/789,308
Filing Date: February 26, 2004
Exhibit 59

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US05/05877

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
- ☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
- ☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
- ☐ filed together with the international application in electronic form.
- ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application
☒ claims Nos. 13,15,27,29,37 and 39

because:

- ☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

- ☒ the claims, or said claims Nos. 13,15,27,29,37 and 39 are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

Please See Continuation Sheet

- ☐ no international search report has been established for said claims Nos. _____
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
See the lack of unity section of the International Search Report (Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-12, 14, 16-26, 28, 30-36, 38 and 40-42

**WRITTEN OPINION OF THE
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Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>12,25</u>	YES
	Claims <u>1-11, 14, 16-24,26, 28, 30-36, 38, 40-42</u>	NO
Inventive step (IS)	Claims <u>12,25</u>	YES
	Claims <u>1-11, 14, 16-24,26, 30-36, 38, 40-42</u>	NO
Industrial applicability (IA)	Claims <u>1-12, 14, 16-26,28, 30-36, 38-42</u>	YES
	Claims <u>NONE</u>	NO

2. Citations and explanations:

Claims 1-9, 11, 14 16-23, 28, 30-33, 36, 38, 40-42 lack novelty under PCT Article 33(2) as being anticipated by US 20020151056 (SASAI et al) 17 October 2002. Citing earlier work, Sasai et al. teach that embryonic stem cells cultured in medium supplemented with retinoic acid differentiate first to neural precursors and then to neurons [0023]. Sasai et al. further teach use of BMP and hedgehog proteins to further differentiate neurons (see claims 13 and 14). Sasai teach the use of a conditioned medium at [0105]. The methods of Sasai et al. produce dopaminergic, cholinergic, GABAergic, and serotonergic neurons [0023, 0184]. Sasai et al. teach carrying out differentiation methods in the presence and absence of substances to be tested for effects on neural differentiation in claims 56-58. Therefore, Sasai et al. anticipate all of the systems and methods of the instant claims.

Claims 1, 3, 4, 10, 11, 16, 18-24, 26 lack novelty under PCT Article 33(2) as being anticipated by Carpenter et al., Exp Neurol. 2001 Dec;172(2):383-97. Carpenter et al. derived multiple types of mature neurons from human embryonic stem cells by a culture method that included retinoic acid, B27 conditioned medium, NT-3 and BDNF, thus anticipating the systems recited in the instant claims.

Claims 14, 28,30, 32-36, 38, 40-42 lack an inventive step under PCT Article 33(3) as being obvious over Carpenter et al., Exp Neurol. 2001 Dec;172(2):383-97. It would be routine experimentation to observe the effects of test substances in a system such as taught by Carpenter et al.